How specific classes of retinal cells contribute to vision: A Computational Model

Evgenia Kartsaki, Bruno Cessac, Gerrit Hilgen, Evelyne Sernagor

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Introduction

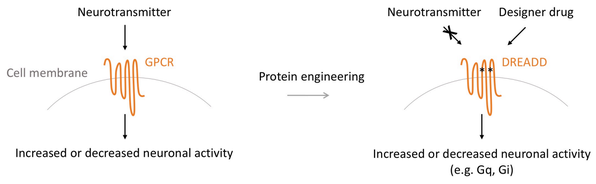
Vision begins with the photoreceptors converting light from the visual scene into electrical signals, compressing our visual world into a code of action potentials sent to the brain by the **retinal ganglion cells** (RGCs). A human retina contains almost **1 million RGCs** and each of these cells interprets **different features** of the visual scene (shape, motion, color, etc.). It is all these **parallel** streams of information received by the brain, that eventually lead to visual perception.
Currently, there exist over 30 RGCs subtypes based on:
- common anatomical features,
- functional properties,
- common gene expression.

Contemporary questions:
✓What role does each RGC subtype play in vision?
✓How is vision impaired if one of these subtypes is inactivated?

☛ We propose a novel approach combining for the first time **pharmacogenetics, electrophysiology, morphology, behavior and mathematical modelling** in order to **selectively inactivate specific RGCs types and decipher their role in vision**, both at the single cell and population level.

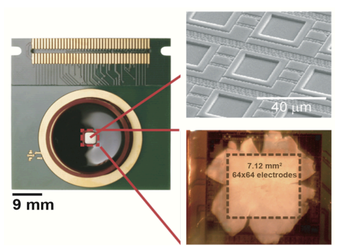
Experiments

Pharmacogenetics: Modify neuronal activity **noninvasively** and **reversibly** by using the **Designer Receptors Exclusively Activated by Designer Drugs** (DREADDs) technique. DREADD-expressing RGCs' activity can be reduced or silenced when the synthetic designer drug clozapine N-oxide (**CNO**) is added to the solution.



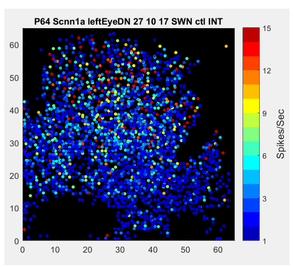
Source: https://benchling.com/pub/dreadds

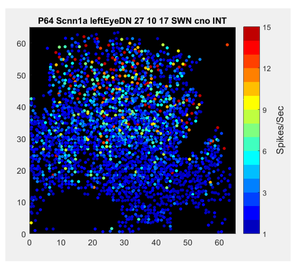
Light stimulation and electrophysiological recordings: Record light responses from the RGC layer at pan retinal level in vitro with the APS MEA in control and CNO conditions



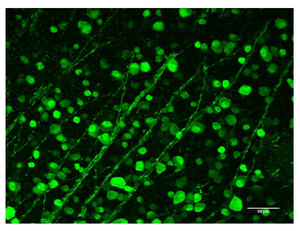
Active Pixel Sensor MEA Chip featuring 4,096 electrodes(42 µm spacing) arranged in a 64x64 configuration, covering an active area of 7.12 mm². From Maccione et al., J Physiol 2014

Pan-retinal recordings in control (left) and CNO (right) conditions

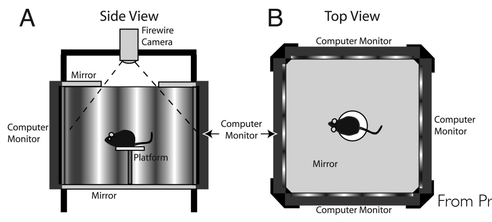




Morphology: Visualize cells and their dendritic trees by imaging under confocal microscopy post-recording.



Behavioral testing: Perform behavioral tests in control and CNO conditions



From Prusky et al., Iovs 2004

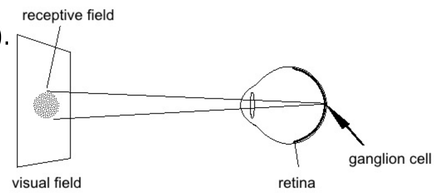
Disclaimer: All the experimental work is done at Pr. Sernagor's lab

Computational analysis

☛ **How does CNO impact the response of RGCs to visual stimuli?**

RGCs response to light stimuli is characterized by their **spatio-temporal receptive field** (RF).

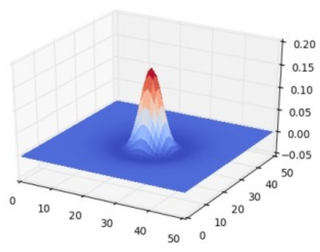
Spatial profile: the region of the visual field in which light stimuli evoke responses in a RGC. The simplest RF is organized into a center-surround structure, responding oppositely to light.
Temporal profile: the temporal course of this response.

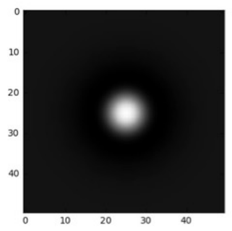


Methods

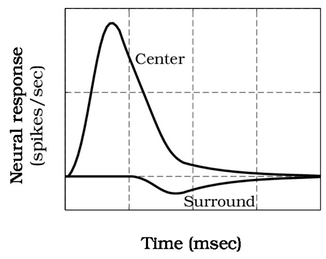
☛ **Use mathematical modelling**

The difference of Gaussians function can model the **spatial** RF





The center-surround mechanism is **temporally** biphasic

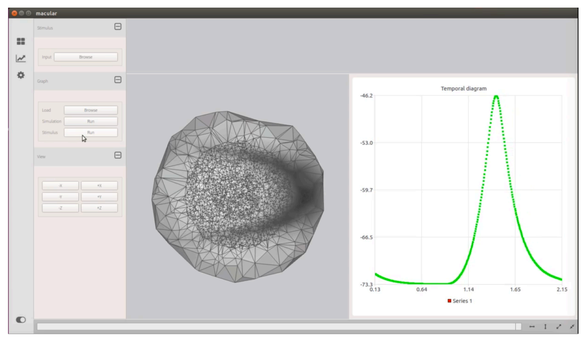


☛ **Use numerical simulations**

PRANAS: A platform for retinal analysis and simulation, developed by the Biovision team at Inria.

MACULAR: A platform for large scale simulations of the retina in pathological conditions (currently under co-development by the Biovision team and the CED engineering team at Inria).

NEURON: A simulation platform for modelling individual and networks of neurons, developed at Yale and Duke.



Macular platform

Temporal profile

Develop a generalized RGC model

Model single cell dynamics with **Hodgkin-Huxley** conductances using the NEURON simulation platform in order to reproduce what we observe in the experiments.

$$C\frac{dV}{dt} = (-g_L(V-V_L) - g_{Na}m^3h(V-V_{Na}) - g_K n^4(V-V_K) - g_{CNO}(V-V_K)$$

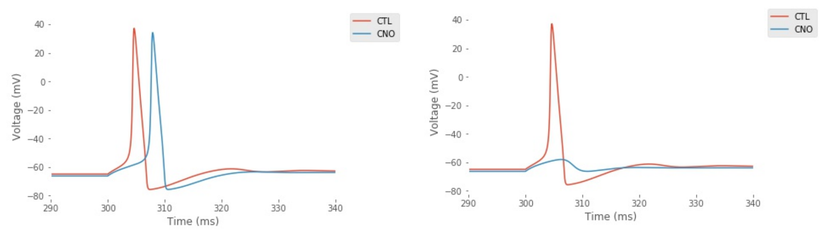
$$\frac{dm}{dt} = a_m(V)(1-m) - m(V)m$$

$$\frac{dh}{dt} = a_h(V)(1-h) - \beta_h(V)h$$

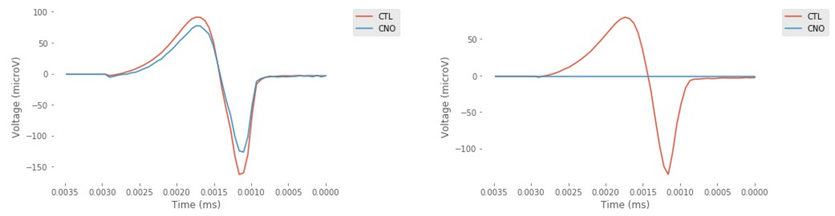
$$\frac{dn}{dt} = a_n(V)(1-n) - \beta_n(V)n$$

To study the effect of CNO on the behavior of the cell, we added a leak potassium channel depended on [CNO], represented by the extra current g_{CNO}.

Simulations



VS Experiments

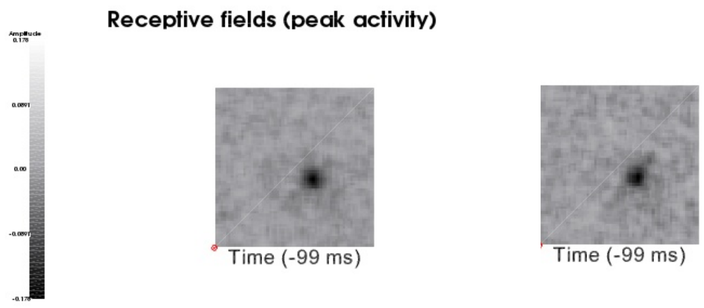


RGC's activity is reduced

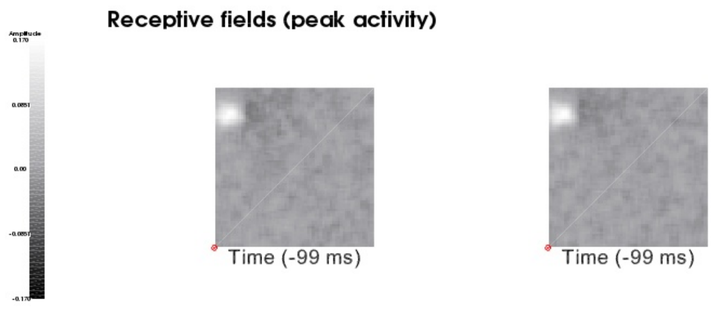
RGC's activity is silenced

Spatial profile

RF estimation using **PRANAS**



Estimated receptive field of an OFF RGC
(A) In control condition (B) In CNO condition



Estimated receptive field of an ON RGC
(A) In control condition (B) In CNO condition

Conclusions

- We reproduced the strong effect of CNO on the temporal part, as in the experiments.
  Next steps:
  -Relate the CNO conductance to the CNO concentration
  -Fit the experimental data, to tune the model's parameters
- There isn't a clear effect on the spatial part yet.
  -There might be, if amacrine cells are also affected by CNO
- Mimic experimental setup with MACULAR.

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